

Osteosarcoma of the mobile spine[†]

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Background: The aims of this analysis were to investigate features and outcome of high-grade osteosarcomas of the mobile spine.

Patients and methods: Since 1977, 20 Cooperative Osteosarcoma Study Group patients had a diagnosis of high-grade osteosarcomas of the mobile spine and were included in this retrospective analysis of patient-, tumor- and treatment-related variables and outcome.

Results: The median age was 29 years (range 5–58). Most frequent tumor sites were thoracic and lumbar spine. All but three patients had nonmetastatic disease at diagnosis. Treatment included surgery and chemotherapy for all patients, 13 were also irradiated. Eight patients failed to achieve a macroscopically complete surgical remission (five local, one primary metastases, two both), six died, two are alive, both with radiotherapy. Of 12 patients with complete remission at all sites, three had a recurrence (two local, one metastases) and died. The median follow-up of the 11 survivors was 8.7 years (range 3.1–22.3), 5-year overall and event-free survival rates were 60% and 43%. Age <40 years, nonmetastatic disease at diagnosis and complete remission predicted for better overall survival (OS, $P < 0.05$).

Conclusions: Osteosarcomas of the mobile spine are rare. With complete resection (and potentially radiotherapy) and chemotherapy, prognosis may be comparable with that of appendicular osteosarcomas.

Key words: chemotherapy, osteosarcoma, outcome, radiotherapy, spine, surgery

introduction

Vertebral osteosarcomas are rare accounting for only 1%–4% of all osteosarcomas [1–4] and 5%–23% of all primary malignant osseous spinal neoplasms [3, 5–7]. Early studies reported a poor prognosis, and treatment was limited [1, 3, 8, 9]. Today en bloc resection and chemotherapy are recommended [10], the role of

radiotherapy remains unclear. Recent studies still observed limited long-time survival [5, 11, 12].

The purpose of this study was to analyze the patient-, tumor- and treatment-related variables and outcomes of patients with primary osteosarcoma of the mobile spine treated according to contemporary osteosarcoma regimens.

materials and methods

In January 2011, the interdisciplinary Cooperative Osteosarcoma Study Group (COSS) had registered 3865 patients with osteosarcoma, and treated in consecutive COSS trials since 1977. All studies were accepted by the appropriate ethics and Protocol Review Committees, respectively. An informed consent was required from all patients or their legal guardians.

For this retrospective study, we searched the COSS database for patients with histologically proven high-grade osteosarcoma of the mobile spine. The mobile spine was defined as cervical, thoracic and lumbar spine. Patients with involvement of the ileum or sacrum were excluded, as were those with low-grade tumors. The first author reviewed all information contained in the COSS database and in the patient files. In the case of

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incomplete information, the contributing centers were requested to provide the missing data.

Evaluation procedures used to define the extension of the primary tumor included conventional radiography in all studies, whereas other methods [computed tomography (CT) scans and magnetic resonance imaging (MRIs)] varied with time and availability. Requirements for exclusion of primary metastases were a negative chest X-ray and a negative bone scan. As of 1991, CT scanning of the chest was also mandatory. During follow-up, radiograms of the chest and the primary tumor were to be repeated at regular intervals specified in the respective protocols.

All patients with high-grade tumors were to be treated according to the same guidelines as patients with extremity tumors with surgery and multidrug chemotherapy. Chemotherapy was carried out following the COSS protocols for high-grade osteosarcomas [13]. After the first trial COSS-77, which was based on postoperative, adjuvant therapy only, all COSS regimens included a uniform treatment concept of preoperative, neoadjuvant chemotherapy followed by surgery of the primary tumor and adjuvant chemotherapy. Details have been reported previously [14–18].

The aim of surgical intervention was complete resection of all tumor manifestations. A complete surgical remission was assumed only when all detectable tumor foci were removed macroscopically complete during first-line therapy. This was assessed separately for local and metastatic disease. A total complete remission was only assumed if a macroscopically complete surgical remission of all tumor sites had been achieved. Response to chemotherapy was assessed histologically according to Salzer-Kuntschik et al. [19]. The distinction between good and poor responses was set at 10% residual viable tumor.

Statistics were calculated using IBM SPSS Statistics software version 20.0 (IBM, Armonk, NY). Overall survival (OS) and event-free survival (EFS) were calculated using the Kaplan–Meier method [20]. The log-rank test was used to compare differences between the survival curves [21]. OS was calculated from the date of diagnostic biopsy until death from any cause and EFS until relapse or death, whichever occurred first. Patients who never achieved a complete surgical remission were supposed to have suffered an event on the first day after biopsy or primary operation if no biopsy was done.

results

Thirty high-grade osteosarcomas involving the mobile spine were identified among 3865 registered patients (0.8%). Ten of these had to be excluded from this analysis: nine had involvement of the sacrum and/or ileum, no sufficient information was available for one. Altogether, 20 patients from 16 institutions in Germany (14), Austria (1) and Switzerland (1), diagnosed in the year 1988–2009, were eligible for this retrospective investigation. Five patients have previously been reported as part of an analysis of osteosarcomas of the spine including the sacrum [22].

In 15 of 20 eligible patients, the histological diagnosis was confirmed by a member of the COSS-reference-pathology-panel. In three patients, local pathologists made the diagnosis, but no material was available for a reference opinion. In two individuals, local pathologists had diagnosed a soft-tissue-sarcoma and a not-otherwise-specified-sarcoma, respectively, but this was revised by a reference review.

Nine patients were female, and 11 eleven male. The median age at diagnosis was 29 years (mean 31, range 5–58), 14 were <40 years. No patient had had prior radiotherapy or suffered from Paget's disease. One osteosarcoma occurred as a second

malignancy following surgically treated urothelial cell carcinoma of the bladder. This patient later went on to develop a third malignancy during osteosarcom therapy, namely papillary carcinoma of the thyroid, which was removed completely.

Information about pain at diagnosis was available for 19 of 20 patients, all of whom presented with pain (median duration: 85 days). Data on neurological dysfunction was available for all patients and it was experienced by nine (median duration: 11 days). A pathologic fracture was recognized in three patients.

Primary tumor sites were cervical ($n = 1$), cervico-thoracic ($n = 1$), thoracic ($n = 9$) and lumbar ($n = 9$) spine. The most frequent subtypes were osteoblastic ($n = 10$) and telangiectatic ($n = 4$) osteosarcoma (Table 1). Tumor volume could be estimated for six patients (median: 120 cm³, range 3–576). Three patients had metastases at diagnosis, all to the lungs and one additionally to distant bones and liver.

All patients underwent resection of their primary tumor, fourteen as primary resection, four following preoperative chemotherapy, one after preoperative chemo- and radiotherapy and one following preoperative radiotherapy alone. The median number of surgical procedures prior to best remission was 2 (range 1–3). Eight patients failed to achieve a total, macroscopically complete surgical remission (five local, one metastases, two both). Local complete macroscopic resection was achieved in 13 individuals, one with residual primary metastases. Local therapy included radiotherapy of thirteen primary tumors, 6 of which were removed incompletely and 7 completely. Median radiation dose was 50 Gy (range: 35–66). Information about radiation-associated acute side effects was obtained for in all 13 irradiated individuals, no toxicities >2 CTCAE v3 were reported.

Systemic treatment included chemotherapy with cisplatin ($n = 20$), doxorubicin ($n = 20$), ifosfamide ($n = 19$) and methotrexate ($n = 16$). Five patients received carboplatin and/or etoposide during primary therapy, too. Gemcitabine was used in one patient due to progressive disease. With the tentative diagnosis of a soft-tissue-sarcoma, one patient received three courses of vincristine and actinomycin D.

Preoperative chemotherapy was used in 5 of 20 patients. Information on response was available for four of them, three had a poor (two grade 4, one grade 6) and one a good response (grade 1).

Of 12 patients with complete remission at all sites, 3 experienced recurrent disease, all within 5 years of diagnosis (2 local, 1 bone metastases) and died. The two patients with local relapse had not received radiotherapy during primary treatment. Of the 5 patients with incomplete surgery of the primary as only cause of residual tumor, 3 died (2 with and one without radiotherapy) and 2 are still alive, 10.0 and 14.2 years after diagnosis, both following radiotherapy.

In April 2012, after a median follow-up of 3.8 years (range 0.7–22.3) for all patients and 8.7 years (range 3.1–22.3) for the survivors, 11 of 20 patients were still alive, nine in first complete surgical remission and two without progression following incomplete surgery and definitive radiotherapy. Among the nine deceased patients, five died of progressive disease without ever having achieved a remission, three of

Table 1. Patient characteristics, treatment and outcomes

No.	Gender	Age (years)	Vertebrae body	Subtype	Primary metastases	Total complete surgical macroscopic remission	Radiotherapy (Gy)	DDP	DOX	IFO	MTX	Other drugs	First event (years from diagnosis)	Status and follow-up (years from diagnosis)
1	F	30	T 10–11	Telangiectatic	None	Yes	+ (47)	+	+	+	+		Metastatic relapse (4.2)	DOD in FR (7.1)
2	M	19	T 1–3	Osteoblastic	None	Yes	–	+	+	+	+		None	NED (10.0)
3	F	5	C 4	Telangiectatic	None	No (local)	+ (50)	+	+	+	+	Carbo, Eto	No CR (local)	NED (14.2)
4	F	19	T 8–10	Chondroblastic	None	Yes	–	+	+	+	+		Local relapse (2.5)	DOD in FR (3.0)
5	M	11	C 7–T2	Osteoblastic	None	Yes	+ (45)	+	+	+	+		None	NED (7.2)
6	M	47	L 5	Small cell	None	No (local)	+ (54)	+	+	+	+	Carbo, Eto	No CR (local)	DOD in PD (2.8)
7	M	20	T 10	Osteoblastic	None	No (local)	+ (45)	+	+	+	+	Eto, VCR, ActoD	No CR (local)	DOD in PD (0.7)
8	M	38	T 6	Osteoblastic	None	Yes	+ (49)	+	+	+	+		None	NED (6.8)
9	F	39	L 3	Unclassified	None	Yes	+ (56)	+	+	–	+		None	NED (2.5)
10	M	50	L 2	Osteosarcoma resembling osteoblastoma	None	No (local)	–	+	+	+	+	Carbo, GEM	No CR (local)	DOD in PD (1.2)
11	M	36	L 5	Unclassified	None	Yes	+ (66)	+	+	+	+		None	NED (3.9)
12	F	58	L 5	Osteoblastic	PUL	No (local, PUL)	+ (60)	+	+	+	–		No CR (local and mets)	DOD in PD (1.0)
13	F	50	L 5	Osteoblastic	None	Yes	–	+	+	+	–		Local relapse (2.7)	DOD in FR (2.8)
14	M	16	T 1–2	Chondroblastoma-like	PUL	No (PUL)	–	+	+	+	+		No CR (mets)	DOC in PD (1.9)
15	M	16	L 2	Telangiectatic	None	Yes	–	+	+	+	+		None	NED (22.3)
16	F	11	T 5–6	Osteoblastic	None	Yes	+ (56)	+	+	+	+		None	NED (3.1)
17	F	18	T 4	Osteoblastic	None	No (local)	+ (45)	+	+	+	+		No CR (local)	NED (10.0)
18	F	52	L 1	Osteoblastic	PUL, OSS, HEP	No (local, PUL, OSS, HEP)	+ (>35)	+	+	+	–	Carbo, Eto	No CR (local and mets)	DOD in PD (1.0)
19	F	57	L 4	Telangiectatic	none	Yes	+ (56)	+	+	+	–		None	NED (2.2)
20	F	28	T 9	Osteoblastic	none	Yes	–	+	+	+	+		None	NED (15.3)

F, female; M, male; C, cervical spinal segment; T, thoracic spinal segment; L, lumbar spinal segment; PUL, pulmonary; OSS, osseous; HEP, hepatic; Gy, Gray; DDP, cisplatin; DOX, doxorubicin; IFO, ifosfamide; MTX, methotrexate; Carbo, carboplatin; Eto, etoposid; VCR, vincristin; ActoD, actinomycinD; GEM, gemcitabine; CR, complete remission; mets, metastases; NED, no evidence of disease; DOD, dead of disease; DOC, dead of complications; PD, primary disease; FR, first relapse.

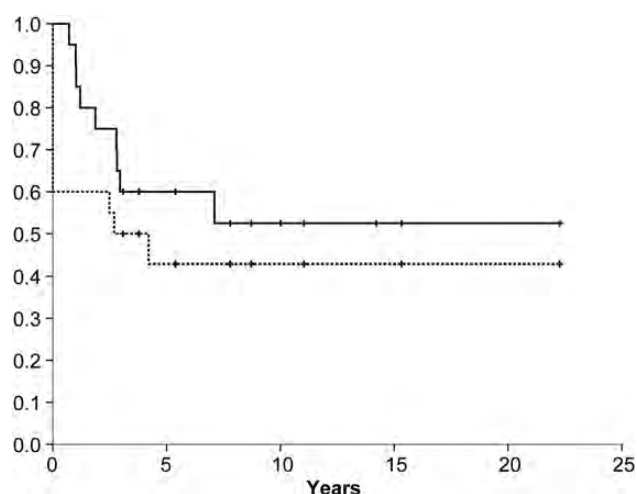


Figure 1. Overall (solid line) (OS) and event-free (dashed line) survival (EFS) of 20 patients with high-grade osteosarcoma of the mobile spine.

recurrence following remission and one due to sepsis during primary therapy.

Actuarial EFS and OS-rates were 43% and 60% after 5 years and 43% and 53% after 10 years, respectively (Figure 1). Age 40 years, primary nonmetastatic disease and local and total complete surgical remission predicted for better OS ($P < 0.05$) and all with the exception of age younger than 40 years also for better EFS ($P < 0.05$) (supplementary Table S1, available at *Annals of Oncology* online). In our cohort, irradiated patients had a 5- and 10-year OS of 69% and 55% and patients without radiotherapy had 43% after 5 and 10 years ($P = 0.57$).

discussion

Information about osteosarcoma of the mobile spine is very limited. To our knowledge, only three series excluding pelvic and sacral tumors have been published [1, 8, 11]. All of them included fewer patients than our study.

Only 0.8% of our registered osteosarcomas were located in the mobile spine, confirming the rarity of this disease [1–4]. The median and mean age of patients in this series was somewhat lower than previously reported in most other series (35–52 years), reflecting the predominantly pediatric constituency of the COSS group [1, 3–6, 9, 11, 12]. None of our patients had a history of prior radiotherapy or Paget's disease. Other series of vertebral osteosarcoma in general have reported up to 30%–40% and more of secondary osteosarcomas [1, 3, 6, 7, 9, 12]. Like in other series, primaries often involved the lumbar vertebrae [1, 3, 6, 7, 8, 9, 12], but a similar proportion of tumors were located in the thoracic spine. This is in accordance with Ilaslan et al. [4] (after excluding the sacrum) and Schwab et al. [11]. Similar to Schwab et al., our rate of metastatic disease at diagnosis was around 15% [11]. Other authors have reported higher rates of 28%–62% [5, 12].

In the 1980s, three 'early' series of vertebral osteosarcoma studied patients managed over a period of 60–80 years. The rates of complete resections and the use of chemotherapy were low. Radiation was mainly palliative [1, 3, 8]. In 1988,

Sundaresan et al. reported 24 patients with vertebral osteosarcoma who were divided into two subgroups. The first encompassed 13 patients treated similar to the 'early' series 1949–1977. The remaining 11 patients, treated in the year 1978–1984, demonstrated a shift toward chemotherapy, complete resection was now achieved in 7 and all but two were irradiated, including completely resected tumors [9].

More recently, three other studies of spinal osteosarcoma were published [5, 11, 12]. In 2010, data from the Surveillance, Epidemiology and End Results Program of 430 vertebral osteosarcomas, including those of the sacrum, were reviewed. Surgical data were available for only 27% of patients of whom 62% underwent resection. Approximately one-third of all primary tumors were irradiated. Data regarding chemotherapy were not presented [5]. In a series from the Massachusetts General Hospital which included 26 patients, treated in the year 1982–2010, 20 underwent surgical procedures and complete en bloc resection was achieved in 7. Radiotherapy was carried out in all but two and multidrug chemotherapy was given to all but one patient [12]. Schwab et al. published 17 patients with osteosarcoma of the mobile spine of whom all received methotrexate- and doxorubicin-based chemotherapy. All but two patients were treated surgically and en bloc resection was achieved in nine. Eight of 17 patients were also irradiated [11]. In summary over the years treatment of vertebral osteosarcoma showed a tendency to increased use of chemotherapy and more aggressive surgery with a higher rate of complete resections and a frequent use of radiotherapy to optimize local control. The patients included in our series were treated similar to those of the other recent series.

The 'early' studies reported very poor survival data [1, 3, 8, 9]. The trend toward more aggressive therapy in more recent series was associated with improved but still limited survival with 5-year survival rates from 18% to 45% [5, 11, 12]. The only reported 10-year survival rate was 8% [5]. We observed more encouraging long-term data: OS expectancies after 5 and 10 years were 60% and 53%, respectively.

While no analyses of prognostic factors were carried out in the 'early' studies, recent analyses have hinted toward such factors. Not surprisingly, we confirmed that primary metastatic disease has negative prognostic implications [5, 11, 23] that the outcome of younger patients is better [23] and that the extent to which a tumor and, if present, its metastases can be removed is of utmost importance (supplementary Table S1, available at *Annals of Oncology* online). The aim of surgery in osteosarcoma in general should always be complete resection of the tumor in an en bloc-approach and ideally with wide and therefore negative margins [24]. Given the site-specific anatomic constraints, appropriate resection margins, however, are particularly difficult to obtain in the mobile spine, and trying to enforce such margins can be associated with significant morbidity [10]. Nevertheless, the well-known relation between margins and local control could also be confirmed for spine sarcomas [25, 26]. The type of resection chosen will impact upon the margins. The rate of local recurrence after piecemeal resections has been shown to be higher than after en bloc resections [25]. En bloc resections provide improved local control [10, 25, 26]. It is still under discussion if this translates into improved OS [11, 12]. Our

data support the impression that en bloc resection should be recommended whenever feasible, as it provides improved local control and probably improved OS [10].

Despite improvements in surgery, inadequate margins or incomplete resections remain to pose a challenge in osteosarcoma of the mobile spine. Radiation can help to provide local control of osteosarcoma in situations with microscopic or minimal residual disease [27]. In accordance with recent recommendations [28], we suggest that radiotherapy should be considered in cases of incomplete resections or inadequate margins. Two of our patients with macroscopically incomplete resection achieved permanent local control following radiotherapy, but this finding should not be misunderstood: the main goal of surgery remains a RO resection with wide margins, not debulking surgery.

Our analysis has certain limitations: retrospectiveness, selection bias, lack of a control group, small number of patients treated during two decades and the limitation of surgical analysis to macroscopic completeness of resection; neither type of resection nor resection margins were evaluated.

Nevertheless, this is probably the most detailed analysis of patient- and tumor-related variables and therapeutic measures ever carried out for osteosarcoma of the mobile spine allowing to identify clinical factors that might predict long-term outcomes and to give recommendations for treatment. Despite including no more than 20 patients, it is, to our knowledge, also the largest analysis of this very rare tumor site.

Using intensive multimodal treatment, we achieved an outcome which was surprisingly favorable. Treatment of this disease remains challenging, but we believe that the results achieved justify aggressive approaches. We recommend treatment by surgery and multidrug chemotherapy according to the same guidelines as for patients with extremity tumors, and that radiotherapy should be added in cases with incomplete or inadequate margins and should at least be considered in all others. With such an aggressive approach, prognosis may become comparable with that of osteosarcoma of the extremities [29].

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disclosure

The authors have declared no conflicts of interest.

references

- Barwick KW, Huvo AG, Smith J. Primary osteogenic sarcoma of the vertebral column: a clinicopathologic correlation of ten patients. *Cancer* 1980; 46: 595–604.
- Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. *Cancer* 2009; 115: 1531–1543.
- Shives TC, Dahlin DC, Sim FH et al. Osteosarcoma of the spine. *J Bone Joint Surg Am* 1986; 68: 660–668.
- Ilaslan H, Sundaram M, Unni KK et al. Primary vertebral osteosarcoma: imaging findings. *Radiology* 2004; 230: 697–702.
- Mukherjee D, Chaichana KL, Gokaslan ZL et al. Survival of patients with malignant primary osseous spinal neoplasms: results from the Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 2003. *J Neurosurg Spine* 2011; 14: 143–150.
- Dreghorn CR, Newman RJ, Hardy GJ et al. Primary tumors of the axial skeleton. Experience of the Leeds Regional Bone Tumor Registry. *Spine (Phila Pa 1976)* 1990; 15: 137–140.
- Kelley SP, Ashford RU, Rao AS et al. Primary bone tumours of the spine: a 42-year survey from the Leeds Regional Bone Tumour Registry. *Eur Spine J* 2007; 16: 405–409.
- Tigani D, Pignatti G, Picci P et al. Vertebral osteosarcoma. *Ital J Orthop Traumatol* 1988; 14: 5–13.
- Sundaresan N, Rosen G, Huvo AG et al. Combined treatment of osteosarcoma of the spine. *Neurosurgery* 1988; 23: 714–719.
- Sciubba DM, Okuno SH, Dekutoski MB et al. Ewing and osteogenic sarcoma: evidence for multidisciplinary management. *Spine (Phila Pa 1976)* 2009; 34: S58–S68.
- Schwab J, Gasbarrini A, Bandiera S et al. Osteosarcoma of the mobile spine. *Spine (Phila Pa 1976)* 2012; 37: E381–E386.
- Schoenfeld AJ, Hornicek FJ, Pedlow FX et al. Osteosarcoma of the spine: experience in 26 patients treated at the Massachusetts General Hospital. *Spine J* 2011; 10: 708–714.
- Bielack S, Jurgens H, Jundt G et al. Osteosarcoma: the COSS experience. *Cancer Treat Res* 2009; 152: 289–308.
- Bielack S, Kempf-Bielack B, Schwenzler D et al. Neoadjuvant therapy for localized osteosarcoma of extremities. Results from the Cooperative osteosarcoma study group COSS of 925 patients. *Klin Padiatr* 1999; 211: 260–270.
- Winkler K, Beron G, Kotz R et al. Neoadjuvant chemotherapy for osteogenic sarcoma: results of a Cooperative German/Austrian study. *J Clin Oncol* 1984; 2: 617–624.
- Winkler K, Beron G, Delling G et al. Neoadjuvant chemotherapy of osteosarcoma: results of a randomized cooperative trial (COSS-82) with salvage chemotherapy based on histological tumor response. *J Clin Oncol* 1988; 6: 329–337.
- Fuchs N, Bielack SS, Epler D et al. Long-term results of the co-operative German-Austrian-Swiss osteosarcoma study group's protocol COSS-86 of intensive multidrug chemotherapy and surgery for osteosarcoma of the limbs. *Ann Oncol* 1998; 9: 893–899.
- Ferrari S, Palmerini E, Staals EL et al. The treatment of nonmetastatic high grade osteosarcoma of the extremity: review of the Italian Rizzoli experience. Impact on the future. *Cancer Treat Res* 2009; 152: 275–287.

19. Salzer-Kuntschik M, Delling G, Beron G et al. Morphological grades of regression in osteosarcoma after polychemotherapy—study COSS 80. *J Cancer Res Clin Oncol* 1983; 106(Suppl): 21–24.
20. Kaplan EL MP. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53: 457–481.
21. Mantel. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966; 50: 163–170.
22. Ozaki T, Flege S, Liljenqvist U et al. Osteosarcoma of the spine: experience of the Cooperative Osteosarcoma Study Group. *Cancer* 2002; 94: 1069–1077.
23. McGirt MJ, Gokaslan ZL, Chaichana KL. Preoperative grading scale to predict survival in patients undergoing resection of malignant primary osseous spinal neoplasms. *Spine J* 2011; 11: 190–196.
24. Picci P, Sangiorgi L, Rougraff BT et al. Relationship of chemotherapy-induced necrosis and surgical margins to local recurrence in osteosarcoma. *J Clin Oncol* 1994; 12: 2699–2705.
25. Talac R, Yaszemski MJ, Currier BL et al. Relationship between surgical margins and local recurrence in sarcomas of the spine. *Clin Orthop Relat Res* 2002; 397: 127–132.
26. Fisher CG, Keynan O, Boyd MC et al. The surgical management of primary tumors of the spine: initial results of an ongoing prospective cohort study. *Spine (Phila Pa 1976)* 2005; 30: 1899–1908.
27. DeLaney TF, Park L, Goldberg SI et al. Radiotherapy for local control of osteosarcoma. *Int J Radiat Oncol Biol Phys* 2005; 61: 492–498.
28. Schwarz R, Bruland O, Cassoni A et al. The role of radiotherapy in osteosarcoma. *Cancer Treat Res* 2009; 152: 147–164.
29. Bielack SS, Kempf-Bielack B, Delling G et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. *J Clin Oncol* 2002; 20: 776–790.